REMARKS

I. Comments on Restriction Requirement

The Examiner maintained the restriction requirement and made it final (Office Action, pages 2-4). The Examiner alleged that the requirement to elect a single SEQ ID NO: was a proper "restriction requirement" and not an "election of species." The Examiner cited MPEP § 803.02, alleging that because Applicants' invention does not fall into the "C-R" format of the example in MPEP § 803.02, the "restriction requirement" was proper. Applicants do not agree with the Examiner's allegations regarding the restriction requirement and reserve the right to petition the final restriction requirement.

Claims 34, 35, 36, 38, and 40 are "method of use" claims, which ultimately depend from product Claim 32, and Claim 37 is a "method of use" claim which ultimately depends from product Claim 26. Therefore, upon allowance of Claim 32, it is believed that Claims 34, 35, 36, 38, and 40 should be rejoined and considered, and upon allowance of Claim 26, it is believed that Claim 37 should be rejoined and considered, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. § 103(b)."

II. Objection to Claims 25-31

The Examiner objected to Claims 25-31 as being "dependent upon non-elected claims." (Office Action, page 4.) Amended Claims 25, 26, and 30 are independent claims, and therefore Applicants respectfully request that the Examiner withdraw the objection to Claims 25-31.

III. Objection to Claims 27, 31, and 32

The Examiner objected to Claims 27, 31, and 32 because they "recite non-elected SEQ ID NO." and stated that "[a]ppropriate correction is required." (Office Action, pages 4-5.)

Applicants traverse this objection. As discussed in *In re Weber*, 198 USPQ 328 (CCPA 1978), it is an applicant's right, by statute, "to claim his invention with the limitations he regards as necessary to circumscribe that invention, with the proviso that the application comply with the requirements of §112." (*Weber* at 331.) The Court has further decided that §112, second paragraph

"allows the inventor to claim the invention as he contemplates it." (*Weber* at 331.) The Court further explained that:

> As a general proposition, an applicant has a right to have each claim examined on the merits. If an applicant submits a number of claims, it may well be that pursuant to a proper restriction requirement, those claims will be dispersed to a number of applications. Such action would not affect the right of the applicant eventually to have each of the claims examined in the form he considers to best define his invention. If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the subgenera would be defined by the examiner rather than by the applicant, it is not inconceivable that a number of the fragments would not be described in the specification. (*Weber* at 331.)

Hence, it is improper for the Examiner to require removing the nonelected species of a Markush Group as a condition for examination of the elected claims and species.

IV. Rejection of Claims 25-33, 39, 41, and 42 Under 35 U.S.C. §101

SUMMARY OF THE INVENTION

Applicants' invention is directed, *inter alia*, to an isolated polynucleotide encoding a regulatory proteins (NHRP), in particular to the elected polynucleotide encoding NHRP-37 (SEQ ID NO:74). The claimed polynucleotide has a variety of utilities, in particular in expression profiling, and in particular for diagnosis of conditions or diseases characterized by expression of NHRP, for toxicology testing, and for drug discovery. (See the Specification at, e.g., page 55, line 4 through page 60, line 27.) As described in the Specification (page 32, lines 18-30):

> NHRP-37 (SEQ ID NO:37) was first identified in Incyte Clone 2507014 from the CONUTUT01 cDNA library using a computer search for amino acid sequence alignments. A consensus sequence, SEQ ID NO:74, was derived from the extended and overlapping nucleic acid sequences: Incyte Clones 2507014 (CONUTUT01), 1394758 (THYRNOT03), 1650580 (PROSTUT09), 2152990 (BRAINOT09), 2361374 (LUNGFET03) and 2602153 (UTRSNOT10).
>
> In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:37. NHRP-37 is 350 amino acids in length and has two potential glycosylation sites at N_{147}TYQ and N_{185}CTQ, and several potential phosphorylation sites as designated by subscripts, S_9LND, S_{17}FAE, T_{80}WKE, T_{122}SR, S_{171}AR, T_{174}GNE, T_{187}QK, T_{237}MID, S_{293}HHD, S_{313}NT$_{315}$ER, S_{329}HLE, S_{340}ETD,

> and T_{342}DRD. NHRP-37 has sequence homology with S. cerevisiae, GI 1322869, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Claims 25-33, 39, 41, and 42 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that "the claimed invention is not supported by either a specific, substantial, credible asserted utility or a well-established utility." (Office Action, page 5.)

The rejection of Claims 25-33, 39, 41, and 42 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue is a polynucleotide corresponding to a gene that is expressed in human tissue. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Applicants submit with this response the Declaration of Bedilion[1] describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Patent Examiner with respect to the utility of the claimed polynucleotide are without merit.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would appreciate that cDNA microarrays that contained the SEQ ID NO:74 polynucleotide would be a more useful tool than cDNA microarrays

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[1]The Bedilion Declaration is filed herewith in unexecuted form. The executed Declaration will be filed as soon as it is available.

> that did not contain the SEQ ID NO:74 polynucleotide in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating immune responses and cancers for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15.)

The Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise function.

A. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end"). *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

B. Uses of the claimed polynucleotide for diagnosis of conditions and disorders characterized by expression of NHRP, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Bedilion Declaration accompanying this response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

1. The uses of the claimed polynucleotide for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion Declaration. The claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Lal '870 application on June 6, 1997 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide

in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications. (Bedilion Declaration, ¶¶ 12 and 15).[2]

In connection with his explanations, Dr. Bedilion states that the "Lal '870 application would have led a person skilled in the art on June 6, 1997 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of immune responses and cancers to conclude that a cDNA microarray that contained the SEQ ID NO:74 polynucleotide would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:74 polynucleotide." (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on June 6, 1997] that cDNA microarrays that contained the SEQ ID NO:74 polynucleotide would be a more useful tool than cDNA microarrays that did not contain the SEQ ID NO:74 polynucleotide in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating immune responses and cancers for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-June 6, 1997 publications showing the state of the art on June 6, 1997. (Bedilion Declaration, ¶ ¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include almost three pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on June 6, 1997 (and for several years prior to June 6, 1997) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be considered and evaluated in connection with the development of the drug" and how the teachings of the Lal '870 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

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[2]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Lal '870 specification, that the claimed polynucleotide would be useful in connection with developing new drugs using technology, such as northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Lal '870 application at the time it was filed "would have wanted their cDNA microarray to have a probe as described in (i) because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to June 6, 1997." (Bedilion Declaration, ¶ 15, item (f).) This, by itself, provides more than sufficient reason to compel the conclusion that the Lal '870 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

Nowhere does the Patent Examiner address the fact that, as described on e.g., at pages 14, lines 21-23, page 56, lines 15-19, page 58, line 8 through page 59, line 28, and page 67, line 21 through page 68, line 14 of the Lal '506 application, the claimed polynucleotide can be used as a highly specific probe in, for example, cDNA microarrays – a probe that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotide. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., <u>they are useful in analyzing compounds</u>)" (emphasis added)).

The Bedilion Declaration shows that a number of pre-June 6, 1997 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Lal '870 application was filed (Bedilion Declaration ¶¶ 10-14;

Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published after the filing of the Lal '870 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
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> * * *
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> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up– or down-regulated is required.
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> * * *
>
> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis in original)

John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Reference No. 1):

In another post-June 6,. 1997 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, (August 1997) Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947 (Reference No. 2) (emphasis added).

2. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., supra (Reference No. 1):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Reference No. 1, page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 3); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology - - potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 4).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107:681-685 (1999) (Reference No. 5, see page 683). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 6), indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be withdrawn regardless of their merit.

3. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or

entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the sequence of the claimed polynucleotide and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotide and its use of that polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

C. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific, substantial, credible" utilities. (Office Action at page 5.) The Examiner is incorrect both as a matter of law and as a matter of fact.

1. The Precise Biological Significance Or Function Of An Expressed Polynucleotide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological significance" (Office Action, page 6) of the claimed

invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15, Bedilion), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or significance of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

2. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polynucleotide encodes a polypeptide expressed by humans, the Examiner refused to impute the utility of the members of the family of expressed polypeptides to NHRP.

In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses NHRP as if the general class in which it is included is not the family of expressed polypeptides, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the family of expressed polypeptides does not. The family of expressed polypeptides is sufficiently specific to rule out any reasonable possibility that NHRP would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the family of expressed polypeptides has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the NHRP encoded by the claimed polynucleotide is useful. It follows that the claimed polynucleotide also is useful.

The Examiner then goes on to assume that the only use for the claimed polynucleotide absent knowledge as to how its encoded polypeptide actually works is further study of the claimed polynucleotide itself.

Not so. As demonstrated by Applicants, knowledge that the claimed polynucleotide encodes a polypeptide expressed by humans is more than sufficient to make it useful for the diagnosis and treatment of diseases associated with cell proliferation, particularly immune responses and cancers. Indeed, NHRP-1, for example, has been shown to be expressed in cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses. The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

3. Because the uses of the claimed polynucleotide in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. [Bedilion Declaration at ¶ 15.]

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include diagnostic assays (e.g., pages 55-59) and chromosomal mapping (e.g., pages 59-60).

4. Irrelevance of differential expression or disease association to utility in toxicology testing

The Examiner argues on pages 7-8 of the Office Action that the specification does not disclose whether the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide, is differentially expressed in different tissues or associated with any disease. This is irrelevant. Applicants need not demonstrate whether the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide is differentially expressed or associated with any disease, only whether the claimed polynucleotide is useful. The claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide is useful whether or not the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide is differentially expressed in any tissues or is associated with any disease.

The claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide can be used for toxicology testing in drug discovery without any knowledge of differential expression or disease association of the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide. Monitoring the expression of the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polynucleotide or polypeptide, regardless of the biological function or differential expression of the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide. The claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide is useful for measuring the toxicity of drug candidates specifically targeted to **other** polynucleotides or polypeptides regardless of any possible utility for measuring the properties of the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide.

D. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to withdraw the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised

Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p. 52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have

found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.C.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.C.2. Thus the Training Materials cannot be applied consistently with the law.

V. Rejection of Claims 25-33, 39, 41, and 42 Under 35 U.S.C. §112, first paragraph, enablement

A. To the Extent the Rejection of the Claimed Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first

paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

B. On the basis of fragments, variants, arrays, complementary sequences, and RNA equivalents

The Examiner further contended that the claimed polynucleotide encoding variants of SEQ ID NO:37, polynucleotides encoding fragments of SEQ ID NO:37, polynucleotide variants of SEQ ID NO:74, fragments of SEQ ID NO:74, fragments of polynucleotide variants of SEQ NO:74, complementary polynucleotide sequences to the above, and arrays comprising the above are not enabled. The Examiner states that "[t]he specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims." (Office Action, page 9.)

The claimed polynucleotide are enabled, i.e., they are supported by the Specification and what is well known in the art.

A. How to make

SEQ ID NO:37 and SEQ ID NO:74 are specifically disclosed in the application (see, for example, pages 95-96 and pages 113-114 of the Sequence Listing). Variants of SEQ ID NO:37 and SEQ ID NO:74 are described, for example, on page 33, lines 1-18. Incyte clones in which the nucleic acids encoding the human NHRP-37 were first identified and libraries from which those clones were isolated are described, for example, on page 32, lines 18-23. Chemical and structural features of NHRP-37 are described, for example, on page 32, lines 24-30.

The Examiner alleged that "even a single amino acid substitution or what appears to be a minor modification will often dramatically affect the biological activity of a protein," and "it could not be predicted that a variant polynucleotide, or polynucleotide encoding a variant protein would have equivalent functional characteristic of the polynucleotide which encodes SEQ ID NO:37." (Office Action, page 11.) However, Applicants submit that the polypeptide variant sequences and polynucleotide variant sequences are described by their being "naturally occurring" and by their

percentage sequence identity with SEQ ID NO:37 and SEQ ID NO:74 and not by biological activity. The choice of amino acids or nucleotides to alter is made by nature. "Naturally occurring" polypeptide variant sequences and polynucleotide variant sequences occur in nature; they are not created exclusively in a laboratory. The Specification teaches how to find polynucleotide variants (e.g., page 55, lines 19-23) which can then be expressed to make polypeptide variants and how to use BLAST to determine whether a given naturally occurring polynucleotide sequence falls within the "at least 95% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74" scope and whether a given naturally occurring amino acid sequence falls within the "at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37" scope (e.g., page 63, line 10 through page 64, line 5). In addition, determination of percentage identity is well known in the art.

The making of the claimed polynucleotide by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g., page 33, line 29 through page 34, line 3, page 36, line 30 through page 37, line 2, and page 37, lines 16-26. The making of the claimed arrays is disclosed in the Specification at, e.g, page 58, line 14 through page 59, line 13, and page 67 line 22 through page 68, line 10. The making of the claimed polynucleotide comprising complementary sequences is disclosed in the Specification at, e.g., page 68, lines 16-25 and page 48, lines 26-29.

Furthermore, in order to expedite prosecution, Claim 32 has been amended to recite:

An isolated polynucleotide selected from the group consisting of. . .

c) a polynucleotide completely complementary to a polynucleotide of a) over the entire length of the polynucleotide of a),

d) a polynucleotide completely complementary to a polynucleotide of b) over the entire length of the polynucleotide of b).

In order to expedite prosecution, Claim 25 has been amended so that polynucleotides encoding a "biologically active fragment" are no longer recited. Therefore the rejection on the basis of polynucleotides encoding biologically active fragments of SEQ ID NO:37 is moot.

Applicants submit that the specification fully enables the making of the claimed polynucleotides encoding immunogenic fragments of SEQ ID NO:37. The polypeptide sequence of SEQ ID NO:37 is

provided in the Sequence Listing. Preparation of immunogenic fragments is described in the Specification, e.g., at page 47, lines 4-10 and page 69, line 22 through page 70, line 2.

The ability of a given fragment to induce a specific immune response in animals or cells, to bind with specific antibodies, or to elicit production of antibodies that bind to the full-length NHRP-37 (See Specification at, e.g., page 12, lines 6-8, page 46, line 22 through page 48, line 14, and page 69, line 21 through page 70, line 6) are tests for whether the fragment is "immunogenic." The tests of fragments by these methods do not require undue experimentation; the specification provides a test for antibody binding e.g., at page 61, lines 13-16.

This satisfies the "how to make" requirement of 35 U.S.C. § 112, first paragraph.

B. How to Use

The claimed polynucleotide variants, fragments, and complementary sequences are products of expressed genes. The claimed arrays comprise expressed genes. Therefore, these polynucleotides and arrays are useful for the same purposes as the polynucleotides comprising the polynucleotide sequence of SEQ ID NO:74 and the polynucleotide encoding the polypeptide sequence of SEQ ID NO: 37. These utilities are described fully under the rejection under §101 (*supra*) of this Response and in the Bedilion Declaration. In addition, the Specification discloses the use of complementary polynucleotides in antisense technology e.g., on page 11, line 25 through page 12, line 3, page 48, lines 16-23, page 49, lines 7-18, page 58, lines 18-26, and page 68, lines 16-25. In addition the Specification discloses the use of arrays e.g., on page 58, line 8 through page 59, line 28 and page 67, line 21 through page 68, line 14. This satisfies the "how to use" requirement of 35 U.S.C. § 112, first paragraph.

The Examiner cited Burgess et al., Lazar et al., Mathews and Van Holde, Matthews, and Bork in support of the argument that the claimed variant polynucleotides and recited variant polypeptides may have different biological functions than SEQ ID NO:74 and SEQ ID NO:37. However, these documents do not support the enablement rejection as the Specification, along with what is well known to one of skill in the art, enable the use of the claimed polynucleotide in toxicology testing by virtue of their being expressed polynucleotides, regardless of their biological function. The Examiner has confused use with biological function.

For at least the above reasons, Applicants respectfully request that the enablement rejections be withdrawn.

VI. Rejection of Claims 25, 28, 29, 30, 32, 33, 39, 41, and 42 Under 35 U.S.C. §112, first paragraph, written description, new matter

The Examiner rejected Claims 25, 28, 29, 30, 32, 33, 39, 41, and 42 under 35 U.S.C. §112, first paragraph, stating that the claims were not adequately described because they allegedly contain "new matter."

A. Variants

The Examiner alleged that "naturally occurring amino sequences at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37" and "a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide selected from the group consisting of SEQ ID NO: 38-74" were not supported in the original disclosure. The Examiner noted that "[t]he specification contemplates allelic sequences on page 10, lines 1-7, and NHRP variants having 90% sequence identity [to] the NHRP sequence, however, this is not adequate basis for naturally occurring amino acid sequences having at least 90% identity to SEQ ID NO:37 or naturally occurring polynucleotide sequences having 90% sequence identity to SEQ ID NO:74." (Office Action, pages 16-17.)

In order to expedite prosecution, Claim 25 is amended to recite "a polypeptide comprising a naturally occurring amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37" and Claim 32 is amended to recite "a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74."

Naturally occurring polypeptide sequences are supported in the Specification, e.g, at page 9, lines 23-26:

> NHRP, as used herein, refers to the amino acid sequences of substantially purified NHRP obtained from any species, particularly mammalian, including bovine, ovine, porcine, murine, equine, and preferably human, from any source whether natural, synthetic, semi-synthetic, or recombinant.

Polypeptides having at least 95% sequence identity to SEQ ID NO:1-37 are supported in the Specification, e.g, at page 33, lines 3-5:

> A most preferred NHRP variant is one having at least 95% amino acid sequence identity to an NHRP disclosed herein (SEQ ID NOs:1-37).

Case law provides that to fulfill the written description requirement of 35 U.S.C. §112, first paragraph, ". . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Consideration of the originally filed application shows that Applicants were in possession of what is now claimed, *i.e.*, "a naturally occurring polynucleotide sequence at least 95% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74."

In this regard, see the following portions of the Specification as well as those cited above:

> It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of nucleotide sequences encoding NHRP, some bearing minimal homology to the nucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of nucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the nucleotide sequence of naturally occurring NHRP, and all such variations are to be considered as being specifically disclosed. (Specification, page 33, lines 11-18.)

> Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular methodology, protocols, cell lines, vectors, and reagents described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. (Specification, page 9, lines 1-6.)

Thus, while the originally filed application does not contain a verbatim recitation of the present "at least 95% identical to a polynucleotide sequence. . ." claim language, it is apparent that the inventors

contemplated naturally occurring polynucleotide sequences of NHRP molecules at least 95% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74 by virtue of contemplating naturally occurring polypeptide sequences of NHRP molecules at least 95% identical to a polypeptide sequence selected from the group consisting of SEQ ID NO:1-37.

Accordingly, the "at least 95% identical to a polynucleotide sequence . . ." language appearing in Claim 32 does not represent new matter.

B. Arrays

The Examiner alleged that Claims 41 and 42 which recite "an array comprising. . . a polynucleotide sequence specifically hybridizable with at least 30 contiguous nucleotides of a target polynucleotide" and "an array . . . complementary to at least 30 contiguous nucleotides" respectively, contained new matter for the recitation of "at least 30 contiguous nucleotides." In order to expedite prosecution, Claim 41 is amended to recite "20 contiguous nucleotides" (supported in the Specification e.g, at page 67, line 26 through page 68, line 2). Claim 42 is canceled.

The Examiner alleged that Claim 39 which recites "a microarray wherein at least one element of the microarray is a polynucleotide of claim 33" contains new matter "due to the length of the oligonucleotide (at least 60 contiguous nucleotide) in the array, and due to the dependence on claim 32, drawn in part to complements of polynucleotides comprising naturally occurring sequences having at least 90% sequence identity to SEQ ID NO:74." (Office Action, page 17.) Claim 39 as amended now depends from new Claim 43 which recites: "[a]n isolated polynucleotide comprising 20 contiguous nucleotides of a polynucleotide of claim 32." Furthermore, the complements of polynucleotides comprising a naturally occurring polynucleotide sequence at least 95% identical to SEQ ID NO:74 are supported in the Specification (see above discussion of polynucleotide sequences having at least 95% sequence identity to . ." and page 12, lines 9-17 and page 68, lines 16-25).

For at least the above reasons, Applicants respectfully request that the new matter rejections be withdrawn.

VII. Further Rejection of Claims 25, 28, 29, 30, and 32 Under 35 U.S.C. §112, first paragraph, written description

Claims 25, 28, 29, 30, and 32 have been further rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. The Examiner alleged that "the written description is not commensurate in scope with the claims drawn to polynucleotides encoding naturally occurring amino acids [*sic*] sequences having 90% sequence identity to SEQ ID NO:37 or polynucleotides comprising a naturally occurring polynucleotide sequences [*sic*] at least 90% identical to SEQ ID NO:74." (Office Action, page 18.) The Examiner further alleged that "neither the common attributes of the genus nor specific examples of species representative of the genus have been described" and [w]ith the exception of SEQ ID NO:74, and the polynucleotides encoding SEQ ID NO:37, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation." (Office Action, page 19.)

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:37 and SEQ ID NO:74 are specifically disclosed in the application (see, for example, pages 95-96 and 113-114 of the Sequence Listing). Variants of SEQ ID NO:37 are described, for example, at page 17, lines 8-16. In particular, the preferred, more preferred, and most preferred SEQ ID NO:37 variants (80%, 90%, and 95% amino acid sequence similarity to SEQ ID NO:37) are described, for example, at page 33, lines 1-5. Incyte clones in which the nucleic acids encoding the human NHRP-37 were first identified and libraries from which those clones were isolated are described, for example, at page 32, lines 18-23 of the Specification. Chemical and structural features of NHRP-37 are described, for example, on page 32, lines 24-30. Given SEQ ID NO:37, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:37 having at least 95% sequence identity to SEQ ID NO:37. Given SEQ ID NO:74, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:74 having at least 95% sequence identity to SEQ ID NO:74. The Specification describes (e.g., page 63, line 10 through page 64, line 5) how to use BLAST to determine whether a given sequence falls within the "at least 95% identical" scope. Immunogenic fragments are described in the Specification, e.g, at page 12, lines 6-8.

There simply is no requirement that the claims recite particular variant and fragment polypeptide or polynucleotide sequences because the claims already provide sufficient structural definition of the claimed subject matter. That is, the polypeptide variants and fragments are defined in terms of SEQ ID NO:37 ("An isolated polynucleotide encoding a polypeptide selected from the group consisting of. . . b) a polypeptide comprising a naturally occurring amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, and c) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-37." The polynucleotide variants and fragments are defined in terms of SEQ ID NO:74 ("An isolated polynucleotide selected from the group consisting of. . . : b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74;" "An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 32.")

Because the recited polypeptide variants and fragments are defined in terms of SEQ ID NO:37, and the recited polynucleotide variants and fragments are defined in terms of SEQ ID NO:37 and SEQ ID NO:74, the precise chemical structure of every polypeptide variant and fragment and every polynucleotide variant and fragment within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Applicants to unduly limit the scope of their claimed invention. Applicants further submit that given the polypeptide sequence of SEQ ID NO:37 and the polynucleotide sequence of SEQ ID NO:74, it would be redundant to list specific fragments. The structures of SEQ ID NO:37 and SEQ ID NO:74 provide the blueprint for all fragments thereof. Listing all possible fragments of SEQ ID NO:37 and SEQ ID NO:74 is, thus, a superfluous exercise which would needlessly clutter the Specification. Accordingly, the Specification provides an adequate written description of the recited polypeptide and polynucleotide sequences.

A. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent Claims 25 and 32 recites chemical structure to define the claimed genus:

> 25. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:. . .
>
> b) a polypeptide comprising a naturally occurring amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37. . .
>
> 32. An isolated polynucleotide selected from the group consisting of. . . :

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74. . .

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:37 and SEQ ID NO:74. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides and polypeptides recited by the claims. Such functional recitations that are included add to the structural characterization of the recited polypeptides and polynucleotides. The polynucleotides and polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

B. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078) (Reference No. 7). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al.

further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to regulatory proteins related to the amino acid sequence of SEQ ID NO:37. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as regulatory proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:37. The "variant language" of the present claims recites, for example, polynucleotides encoding "a polypeptide . . . comprising a naturally occurring amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37" (note that SEQ ID NO:37 has 350 amino acid residues). This variation is far less than that of all potential regulatory proteins related to SEQ ID NO:37, i.e., those regulatory proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:37.

C. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of June 6, 1997. Much has happened in the development of recombinant DNA technology in the 17 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:37 and SEQ ID NO:74, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotides encoding

polypeptide variants and polypeptide fragments, the claimed polynucleotide variants, and the claimed polynucleotide fragments at the time of filing of this application.

D. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:37 or SEQ ID NO:74. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

VIII. Rejection of Claims 25-33, 39, 41, and 42 Under 35 U.S.C. §112, second paragraph

The Examiner rejected Claims 25-33, 39, 41, and 42 under 35 U.S.C. § 112, second paragraph, alleging that they are "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Office Action, page 19.)

A. Claims 25-31:"Naturally-occurring"

The Examiner alleged that the phrase "a naturally-occurring amino acid sequence at least 90% identical to an amino acid sequence" of unelected Claim 23 (from which Claims 25-31 formerly depended) rendered Claims 25-31 indefinite. (Amended Claims 25 and 26 are independent claims.) The Examiner stated that "[i]s is unclear how the origin of the polypeptide, natural versus synthetic, can alter the properties of a polynucleotide which would encode said polypeptide." (Office Action, page 20.)

Applicants submit that the recitation of "naturally occurring amino acid sequence" in Claim 23 defines **where to find** the amino acid sequences encompassed by the claim. The use of the term "naturally-occurring" distinguishes an amino acid sequence that occurs in nature from synthetic or engineered amino acid sequences that are created through manual genetic manipulations. The term "naturally occurring amino acid sequence" thus defines the origin of the amino acid sequence (i.e., even though one could theoretically make the polypeptides having at least 95% sequence identity to SEQ ID NO:37 in the laboratory by randomly mutating the human sequence to form a "mutein," the recited "naturally occurring amino acid sequence" must be one that is found in nature). Applicants note that the origin of the amino acid sequence of the polypeptide encoded by the claimed polynucleotide is what is defined by "naturally-occurring" and not the "origin of the polypeptide" (Office Action, page 20) itself. One skilled in the art would understand the meaning of the term "naturally-occurring amino acid sequence" within the context of Claim 23. Moreover, this is standard claim language in claims drawn to polypeptides and polynucleotides, and its use in the instant Claim 23 is entirely consistent with its use in numerous issued U.S. patents, including those of the assignee Incyte as well as in patents of others.

B. Claim 32: "Naturally-occurring"

The Examiner alleged that the phrase "a polynucleotide comprising a naturally-occurring polynucleotide sequence at least 90% identical to a polynucleotide. . ." of Claim 32 rendered Claim 32 indefinite. The Examiner stated that "[i]s is unclear how the origin of the polynucleotide comprising a naturally occurring sequence influences the propertied [*sic*] of the claimed polynucleotides," and "[f]urther, the metes and bounds of the claims cannot be determined as it is unclear if 'naturally occurring' is meant to exclude only chemically synthesized polynucleotides, or if 'naturally occurring' also excludes recombinant polynucleotides which have been replicated in a cell or mRNA which has been expressed from a vector." (Office Action, page 20.)

Applicants submit that the recitation of " naturally-occurring polynucleotide sequence" in Claim 32 defines **where to find** the polynucleotide sequences encompassed by the claim. The use of the term "naturally-occurring" distinguishes a polynucleotide sequence that occurs in nature from synthetic or engineered polynucleotide sequences that are created through manual genetic manipulations. The term "naturally occurring polynucleotide sequence" thus defines the origin of the polynucleotide sequence

(i.e., even though one could theoretically make the polynucleotides having at least 95% sequence identity to SEQ ID NO:74 in the laboratory by randomly mutating the human sequence, the recited "naturally occurring polynucleotide sequence" must be one that is found in nature). Applicants note that the origin of the polynucleotide sequence of the claimed polynucleotide is what is defined by "naturally-occurring" and not the "origin of the polynucleotide" (Office Action, page 20) itself. One skilled in the art would understand the meaning of the term "naturally-occurring polynucleotide sequence" within the context of Claim 32. Moreover, this is standard claim language in claims drawn to polypeptides and polynucleotides, and its use in the instant Claim 32 is entirely consistent with its use in numerous issued U.S. patents, including those of the assignee Incyte as well as in patents of others.

C. Claims 25, 28, 29, and 30: "Biologically active" and "Immunogenic"

The Examiner rejected Claims 25, 28, 29, and 30 alleging that the terms "biologically active" and "immunologically active" are not defined.

In order to expedite prosecution, Applicants have amended Claims 25, 28, 29, and 30 such that "biologically active fragment" is not recited.

Applicants note that the Examiner rejected Claims 25, 28, 29, and 30 on the basis of alleged lack of definition of the phrase "immunologically active" although this phrase does not appear in Claims 25, 28, 29, and 30 or in Claim 23, from which Claims 25, 28, 29, and 30 depend. The Examiner did not allege that the term "immunogenic," which does appear in Claim 23, was not defined. Nevertheless, "immunologically active" as well as "immunogenic" are adequately defined, based on the Specification (e.g., page 12, lines 5-8, page 46, line 27 through page 48, line 14, and page 69, line 21 through page 70, line 6) and what is known by one of skill in the art. The Examiner has presented no evidence to suggest that one of skill in the art would not understand the claims.

D. Claim 32: "RNA equivalent"

The Examiner rejected Claim 32, alleging that "Claim 32 (part e) is vague and definition [*sic*] in the recitation of 'an RNA equivalent' as the specification does not contain a definition for what constitutes said 'equivalent." It is unclear if the claim is intended to encompass RNA species which

differ from the disclosed DNA sequences by more than the substitution of U for all Ts." (Office Action, page 21.)

Applicants have amended Claim 32 to delete the phrase "an RNA equivalent of a)-d)." The word "polynucleotide" covers both DNA and RNA (See e.g., Specification, page 15, lines 6-8) and therefore the claim as amended covers both DNA and RNA in any case.

E. Claim 41: "Specifically hybridizable"

The Examiner rejected Claim 41 for reciting the phrase "specifically hybridizable," alleging that "[i]t is unclear what degree of complementarily [*sic*] is encompassed by 'specifically hybridizable.'" (Office Action, page 21.)

In order to expedite prosecution, Claim 41 is amended to:

> An array comprising different nucleotide molecules affixed in distinct physical locations on a solid substrate, wherein at least one of said nucleotide molecules comprises a first oligonucleotide or polynucleotide sequence completely complementary to 20 contiguous nucleotides of a target polynucleotide, and wherein said target polynucleotide is a polynucleotide of claim 32.

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the indefiniteness rejections.

IX. Rejection of Claim 32 Under 35 U.S.C. §102(b) as Being Anticipated by the New England Biolabs Catalog

The Examiner rejected Claim 32 under 35 U.S.C. §102(b) as being anticipated by the New England Biolabs Catalog. In order to expedite prosecution, Claim 32 has been amended as follows:

> . . . c) a polynucleotide completely complementary to a polynucleotide of a) over the entire length of the polynucleotide of a),
> d) a polynucleotide completely complementary to a polynucleotide of b) over the entire length of the polynucleotide of b). . .

The New England Biolabs Catalog does not teach a polynucleotide completely complementary to a polynucleotide of a) over the entire length of the polynucleotide of a) or a polynucleotide

completely complementary to a polynucleotide of b) over the entire length of the polynucleotide of b). Therefore, the New England Biolabs Catalog does not anticipate Claim 32, and Applicants respectfully request that the Examiner withdraw the novelty rejection of Claim 32.

X. Provisional Rejection of Claims 25, 28, 29, 30, 32, 33, 39, 41, and 42 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting Over Claims 1, 5, 6, and 7 of Copending Application No. 09/539,800

The Examiner rejected Claims 25, 28, 29, 30, 32, 33, 39, 41, and 42 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1, 5, 6, and 7 of 1

copending application No. 09/539,800. Applicants request that the requirement for submission of a Terminal Disclaimer be held in abeyance until such time as there is an indication of allowable subject matter.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections and rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent at (650) 845-4646.

Please charge Deposit Account No. **09-0108** in the amount of **$ 194.00** as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: January 27, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph beginning at page 59, line 4 has been amended as follows:

In another aspect, the oligomers may be synthesized on the surface of the substrate by using a chemical coupling procedure and an ink jet application apparatus, as described in PCT application WO95/25116 [WO95/251116] (Baldeschweiler et al.) which is incorporated herein in its entirety by reference. In another aspect, a "gridded" array analogous to a dot (or slot) blot may be used to arrange and link cDNA fragments or oligonucleotides to the surface of a substrate using a vacuum system, thermal, UV, mechanical or chemical bonding procedures. An array may be produced by hand or using available devises (slot blot or dot blot apparatus) materials and machines (including robotic instruments) and contain grids of 8 dots, 24 dots, 96 dots, 384 dots, 1536 dots or 6144 dots, or any other multiple which lends itself to the efficient use of commercially available instrumentation.

IN THE CLAIMS:

Claim 42 has been canceled.

Claims 25, 26, 30, 32, 39, and 41 have been amended as follows.

Claim 43 has been added.

25. (Once Amended) An isolated polynucleotide encoding a polypeptide [of claim 23] selected from the group consisting of:

a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-37,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, and

c) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-37.

26. (Once Amended) An isolated polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-37 [of claim 24].

30. (Once Amended) A method of producing a polypeptide encoded by a polynucleotide of claim 25 [of claim 23], the method comprising:

d) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide of claim 25 [encoding the polypeptide of claim 23], and

e) recovering the polypeptide so expressed.

32. (Once Amended) An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% [90%] identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74,

c) a polynucleotide completely complementary to a polynucleotide of a) over the entire length of the polynucleotide of a), and

d) a polynucleotide completely complementary to a polynucleotide of b) over the entire length of the polynucleotide of b) [, and

e) an RNA equivalent of a)-d)].

39. (Once Amended) A microarray wherein at least one element of the microarray is a polynucleotide of claim 43 [33].

41. (Once Amended) An array comprising different nucleotide molecules affixed in distinct physical locations on a solid substrate, wherein at least one of said nucleotide molecules comprises a first oligonucleotide or polynucleotide sequence completely complementary to [specifically hybridizable with at least 30] 20 contiguous nucleotides of a target polynucleotide, and wherein said target polynucleotide is a polynucleotide of claim 32.